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08/765,324

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/765,324	12/24/96	KOREN	

EXAMINER: E OMRF143-CIP2

HM21/1020

PATREA L. PABST
ARNALL GOLDEN & GREGORY
2800 ONE ATLANTIC CENTER
1201 WEST PEACHTREE STREET
ATLANTA GA 30309-3450

ART UNIT	PAPER NUMBER
1645	11

DATE MAILED: 10/20/98

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 7-27-98

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire three month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 15-18, 20-23, 25, 27-30, 35-37, 41, 42 and 45-47 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 15-18, 20, 25, 27-30, 35, 41, 42 and 45-47 is/are rejected.
☒ Claim(s) 21, 22, 36-37 is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

★ U.S. GPO: 1996-421-632/40206

Response to Amendment

1. The amendment and declaration filed 7-27-98 have been entered into the record.

2. The Group and/or Art Unit of U.S. Patent application SN 08/765,324 has changed. In order to expedite the correlation of papers with the application please direct all future correspondence to Technology Center 1600, Group 1640, Art Unit 1645.

3. The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

Rejections Maintained

Double Patenting

4. Applicant is advised that should claim 18, 20, 21, and 22, be found allowable, claims 35, 36, and will be rejected under 35 U.S.C. 101 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to reject the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

5. The rejection of claims 42 and 45-47 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is maintained for reasons made of record in Paper No. 7, mailed 1-21-98.

As to claims 42, 45-47, upon review of the application, no support for these claims can be found. Applicant is invited to point to the specification by page and line number where written

description support for these new filed claims can be explicitly found. These claims were not originally filed with the international application and have no written description basis in the claims of the international application as originally filed. The passages which are pointed to by applicants support a variety of immunoassay formats but fail to support the language of these claims determining the ration of LDL to HDL using not cross-reactive antibodies. Although, applicants have provided sufficient evidence to support non-immobilized antibodies in regard to claims 15-17, claims 42 and 45-47 have no written description support in the specification.

6. Claim 15-18, 20-23, 25, 27-30, 35-37, 42 and 45-47, are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is maintained in part and overcome in part.

As to claims 15, 16, 17, the claims are missing essential steps which are required to be able to specifically detect the instantly claimed fractions. For example in claim 15, Apo C-III associated with VLDL or HDL is measured in order to determine the ratio of VLDL to HDL. The specification specifically recites an immobilization of one of the antibodies because in the absence of a separation step or immobilization step, the recited antibodies would not specifically detect the indicated fraction because Apo C-III is present on both VLDL and HDL and thus *the particles which bind both APO C-III and pan B must be separated from the lipoprotein mixture* and particles which bind both Apo C-III and Apo A-I must be separated from the lipoprotein mixture or the amount of Apo C-III associated with HDL or VLDL can not be determined. The function of these assay requires that the antibodies be immobilized in order to function to separate the indicated fraction. Absent immobilization of the antibodies, the assay will not specifically detect the claimed fractions and thus, will not work. Similar reasoning can be applied

to claims 16, 17, 42, and 45-47. In the absence of further guidance from applicants and that the specification requires that particular antibodies must be immobilized for the assay to operate, it would require undue experimentation on the part of the skilled artisan to make and use the assay as instantly claimed and the claims should be so limited is maintained for reasons made of record.

Applicants' amendment and remarks have been carefully considered but are insufficient to overcome the rejection because the claims fail to indicate that the lipoprotein particles *the particles which bind both APO C-III and pan B must be separated from the lipoprotein mixture*. Currently, the claims recite "the complexed antibody-lipoprotein particles", and proper antecedent basis for the term resides in the first complex formation (i.e. APO-CIII containing lipoprotein particles). The separation must include the Pan B antibody. Currently the Pan B antibody is contacted to the biological sample and not the complex formed by the antibody of the Apo C-III and the Apo C-III containing lipoprotein, if both are not separated then one skilled in the art could not determine the amount of Apo C-III associated with Apo B in the same lipoprotein particle. Applicants assert that claim 17 does not need a separation step, this is not persuasive because it is not apparent how a ratio is determined in the absence of such a step. Clarification is requested.

7. Claims 15-17, 30, 41, 42, and 45-47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As to method claims 15, 16, 17, 42, 45-47, the claims are so confusing as to when each antibody is being added wether the antibodies are added together or separate or if the sample is

separated into two aliquot or processed in the same sample. Applicants have not apparently addressed this rejection and therefore it is maintained.

As to claim 30, the claim remains confusing because the terms lack antecedent basis in the independent claim 18. It is noted that applicants have amended claims 28 and 29 appropriately. The examiner suggests that a similar amendment to this claim would obviate this rejection. Thus, it remains unclear as to how the antibodies of the dependent claim relate to the independent claim 18.

As to claim 41, the claim is rendered indefinite because it depends from a canceled claim.

8. Claim 17 is rejected under 35 U.S.C. § 102(b) as being anticipated by Koren et al (Atherosclerosis, 95:157-170, 1992; herein after referred to as Koren A) or Koren et al (Clin Chem, 33(1):38-43, 1987, herein after referred to as Koren B).

Applicants indicate that Koren A or Koren B are not prior art since it does not teach reacting with both LPA-I and LPA1:A-II lipoprotein particles. This is not persuasive both of these particles are in the sample and all the claim requires is that the anti-Apo AI is contacted with the sample to form complexes with both LPA-I and LPA-I:A-II and determining the quantity of total Apo A-II (i.e. that associated with the LPA-I and LPA-I:A-II in the sample) and as such the claim limitation is met. See the recited sections of the articles. The rejection is maintained.

New Rejections

9. Claims 18, 20, 27, 28, 29 and 35 are rejected under 35 U.S.C. 102(b) as being anticipated by Koren et al (Biochimica et Biophysica Acta, 876:91-100, 1986; herein after called

Koren AR) or Koren et al (Biochimica et Biophysica Acta, 876:101-107, 1986; herein after called Koren AS).

Koren AR and Koren AS teach the monoclonal antibody D6, which Koren AR conclude that the D6 monoclonal antibody most likely binds to a rather stable domain of apolipoprotein B that is not altered by the interaction with lipids or polymorphism of the apolipoprotein B (see Koren AS, abstract) and binds and purifies the appropriate lipoproteins from human plasma (see Koren AR, abstract). Koren AR and Koren AS teach the use of the D6 antibody in immunoassays (see binding studies on page 93-94 of Koren AR) or as a capture or immunoabosrbent (see Koren AS, see page 102 coupling of antibodies to agarose, immunoaffinity column and immunoaffinity chromatography). Koren AS teach that the D6 monoclonal antibody specifically binds LDL (see page 104).

10. Claims 18, 20, 23, 25, 27, 28, 29, 30 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koren et al (Biochimica et Biophysica Acta, 876:91-100, 1986; herein after called Koren AR) or Koren et al (Biochimica et Biophysica Acta, 876:101-107, 1986; herein after called Koren AS) as applied to claims 18, 20, 23, 25, 27, 28, 29 and 35 above, and further in view of Koren et al (Atherosclerosis, 95:157-170, 1992; herein after referred to as Koren A).

Koren AR and Koren AS teach the monoclonal antibody D6, which Koren AR conclude that the D6 monoclonal antibody most likely binds to a rather stable domain of apolipoprotein B that is not altered by the interaction with lipids or polymorphism of the apolipoprotein B (see Koren AS, abstract) and binds and purifies the appropriate lipoproteins from human plasma (see Koren AR, abstract). Koren AR and Koren AS teach the use of the D6 antibody in immunoassays (see binding studies on page 93-94 of Koren AR) or as a capture or immunoabosrbent (see Koren AS, see page 102 coupling of antibodies to agarose,

immunoaffinity column and immunoaffinity chromatography). Koren AS teach that the D6 monoclonal antibody specifically binds LDL (see page 104).

Koren A teach monoclonal antibodies which bind Apo-AI, Apo-AII, Apo-CIII, Apo-B, pan Apo-B and specifically identify CDb5, AbA3, EfD3 and standards to measure lipoprotein particles (see pages 161-165, see sections entitled *Analytical procedures, Enzyme-linked immunosorbent assay of lipoprotein particles containing apo A-I, Principle of the method, Monoclonal "pan" apo B antibody and biotinylated polyclonal antibody to apo B, Primary standards, Secondary standards and controls and Details of the method*). Koren A teach that there are reports that indicate the potential clinical significance of certain lipoprotein subspecies are either atherogenic or antiatherogenic (see page 157, summary).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to assemble the lipoprotein and apolipoprotein reagents of Koren AS or Koren AR together with Koren A in a single composition or kit format because Koren A teaches that apolipoproteins, lipoproteins and associated cholesterol are likely medically important parameters and the assembly of reagents in a kit format to detect likely medically important parameters is routine and conventional in the art. It also would have been prima facie obvious to make other monoclonal and recombinant antibodies which bind Apo AI, Apo AII, Apo C-III and Apo E by substitution available apolipoproteins using the antibody production methods and screening characterization methods of Koren AR to arrive at other monoclonal antibodies which bind the other apolipoproteins inasmuch as the immunization and screening methods as admitted and argued by applicant are highly routine in the art said substitutions would not constitute undue experimentation.

11. Claims 18, 20, 27 and 35 rejected under 35 U.S.C. § 102(b) as being anticipated by Marcel et al (J Lipid Res, 28(7):768-77, 1987).

Marcel et al teach a series of monoclonal antibodies which map to three distinct epitopes on apolipoprotein A-I which are all expressed on all HDL particles indicating that several domains exist on apoA-I which have the same conformation on all apoA-I containing lipoproteins. Marcel et al teach an immunoprecipitation reaction using these monoclonal antibodies. Marcel et al also teach that the epitopes are both expressed on all lipoproteins and located in thermo-dynamically stable regions of the molecules. Specifically the 4H1 series of antibodies inherently bind a stable, conformationally independent epitope which is uninfluenced by the lipid content of a specific lipoprotein, apolipoprotein or lipid associated with a specific lipoprotein.

12. Claims 18, 20, 23, 25, 27, 28, 29, 30 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Marcel et al (J Lipid Res, 28(7):768-77, 1987). as applied to claims 18, 20, 27 and 35 above and further in view of Koren et al (Atherosclerosis, 95:157-170, 1992; herein after referred to as Koren A).

Marcel et al (J Lipid Res, 28(7):768-77, 1987) is set forth above. Marcel fail to teach the additional reagents.

Koren A teach monoclonal antibodies which bind Apo-AI, Apo-AII, Apo-CIII, Apo-B, pan Apo-B and specifically identify CDb5, AbA3, EfD3 and standards to measure lipoprotein particles (see pages 161-165, see sections entitled *Analytical procedures, Enzyme-linked immunosorbent assay of lipoprotein particles containing apo A-I, Principle of the method, Monoclonal "pan" apo B antibody and biotinylated polyclonal antibody to apo B, Primary standards, Secondary standards and controls and Details of the method*). Koren A teach that there are reports that indicate the

potential clinical significance of certain lipoprotein subspecies are either atherogenic or antiatherogenic (see page 157, summary).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to assemble the lipoprotein and apolipoprotein reagents of Marcel et al together with Koren A in a single composition or kit format because Koren A teaches that apolipoproteins, lipoproteins and associated cholesterol are likely medically important parameters and the assembly of reagents in a kit format to detect likely medically important parameters is routine and conventional in the art.

Status of Claims

13. Claims 21, 22, 36 and 37 are objected to as depending from rejected base claims. All other claims stand rejected.

14. Any references cited herein but not provided are cited on the PTOL-1449 of October 28, 1997 and thus are presumed available to applicants representative.

Conclusion

15. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy, Ph.D. whose telephone number is (703) 305-7555. The examiner can normally be reached on Monday-Friday from 6:30 AM to 3:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached at (703) 308-3995.

Patricia A. Duffy, Ph.D.
October 13, 1998

Patricia A. Duffy, Ph.D.
Primary Examiner
Group 1600